FACTORS LEADING TO DIGESTIVE DISORDERS IN THE ELDERLY

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The health problems of the aged are compounded of the universal consequences of biological aging and the cumulative effects of chronic diseases, many of these with long periods of latency, which also affect younger individuals. I shall attempt to identify the principal factors leading to digestive disorders in our aging population, limiting the consideration of extrinsic causes to those of high prevalance. Disorders of the liver and the pancreas will not be considered.

In my view, the common and important digestive conditions in aged individuals are chiefly determined by four factors: atheromatosis, both generalized and of the mesenteric vessels, epithelial atrophy and dedifferentiation, degenerative changes in connective tissue, and neuronal degeneration in the autonomic and enteric nervous systems. These primary processes have numerous interactions, as well as secondary consequences such as bacterial overgrowth in the small bowel). Only a few of their probable consequences for the aging gut have been adequately studied. I shall try to specify major gaps in our knowledge, identify research opportunities, and offer some clearly labelled hypotheses.

ATHEROMA

Arteriosclerosis, so nearly universal among the aged in our society, has many well-recognized effects on the digestive tract. The clinical consequences of acute thromboembolic disease of the mesenteric vessels with infarction of the bowel have long been well known. In recent years the syn-

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dromes resulting from incomplete occlusion of these vessels, often compounded by reduced cardiac output (the "low flow states") have been increasingly recognized.[1] The splanchnic circulation, in comparison with other regional vascular systems, receives the largest fraction of the cardiac output and has the highest blood volume, the highest rate of blood flow, and the lowest vascular resistance. It is in turn especially susceptible to reduction in volume and flow during hypoxic or hypovolemic states. Thus hemorrhage, congestive heart failure, hypotension from any cause, anemia, and pulmonary insufficiency all influence the functional and morphological integrity of the gut in old age.

The mucosa, which has much higher oxidative metabolism than the other layers of the gut wall, is principally affected in low flow states, with effects clinically recognized as ischemic colitis or stricture of the small bowel. Numerous instances of classical "abdominal angina" have been reported, and a few in which painless cachexia, due to malabsorption,[2] has been relieved by surgical bypass of partially obstructed mesenteric arteries. But are "cardiac cachexia" and malabsorption in the elderly principally due to ischemia of the mucosa? This is far from clear, and is a matter of much more than theoretical interest.

Another phenomenon now attributed by some to mucosal hypoxia is the development of angiodysplasia of the intestine, recently shown to be one of the leading causes of gastrointestinal bleeding in the elderly.[3] The association of the lesions with aortic stenosis supports this hypothesis. Further, they are most commonly found in the cecum and ascending colon, where the oxygen tension in the mucosa is at the lowest level in the entire intestinal tract.

Both in the brain and in peripheral nerves, the effects of ischemia on neuronal structure and function are well known, yet the consequences of ischemia for the enteric neurons of the myenteric and submucosal plexuses have received little attention. Recently Devroede described[4] a number of patients with rectal incontinence who had well documented abnormalities of neuromuscular function associated with atheromatous narrowing of the inferior mesenteric and hemorrhoidal arteries, and who regained continence when blood flow to the rectum and anus was improved by arterial grafts. It seems likely that among elderly individuals disorders of intrinsic neural function elsewhere in the gut may be attributable in part to circulatory insufficiency. This hypothesis, in my view, deserves extensive study.

EPITHELIAL ATROPHY AND DEDIFFERENTIATION

The apparent stability of the epithelial cell population of the intestinal mucosa has been shown to result from a precisely maintained balance of cell division and cell destruction or loss, in a dynamic process of cell renewal.[5] Evidence from various animal species indicates that cell division is slowed in old age, especially through prolongation of that portion of the cycle (G-1) that precedes the synthesis of DNA in cells soon to divide. The overall result is a population slightly reduced in numbers (atrophy) with an excess of postmature cells. This phenomenon may not be the principal determinant of atrophic states in the elderly because their variability in degree and in time of occurrence is so great as to suggest that extrinsic influences are important. For example, the decline in gastric secretion of hydrochloric acid in older population samples is not attributable to gradual slowing of secretion in each individual, but results from the development of gastric atrophy and achlorhydria in an increasing fraction of the cohort as time goes by.

It now seems clear that, in the stomach at least, atrophy and dedifferentiation are chiefly due to the cumulative effects of repeated superficial chemical injury and repair. The tall columnar cells of the free surface of the epithelium and of the pits (or foveolae) are susceptible to injury by a variety of substances which are unionized and lipid-soluble at acid pH; these include aspirin, other anti-inflammatory agents, ethanol, urea, and (probably most frequently) the bile acids. Once the outer membranes of these cells have been breached, as Davenport originally showed,[6] secreted gastric hydrochloric acid can reenter the mucosa and produce further damage. The loss of surface epithelial cells leads to repair processes similar to the healing of a skin abrasion, in which cells from deeper layers of the gastric glands proliferate to cover the defect. In the associated acceleration of DNA synthesis and cell division, the differentiation of mature cells is suspended or retarded. Hence the rates of cell renewal and destruction are both elevated, but the histologic picture is one of atrophy and loss of highly differentiated components.

This process, atrophic gastritis, is believed to be perpetuated in part by autoimmune mechanism, triggered by the contract of mucosal lymphocytes and plasma cells with the intracellular proteins of injured epithelium. The complement-activated destruction of mature epithelial cells is quite analogous to the mechanism of acquired hemolytic anemia, and has been shown to be similarly inhibited by corticosteroids.[7] Though I have primari-

ly emphasized cumulative injury due to extrinsic (e.g., ethanol) or ectopic (e.g., bile acid) substances, the contribution of biological aging to this type of morphologic change cannot be excluded. Among 24 "normal" Australian men aged 60 to 87 (none were alcoholics and none had gastric symptoms) gastric biopsies showed atrophic gastritis of some degree in 23[8].

In the small and large intestines, the mucosa is not so heavily exposed to extrinsic noxious agents, though it is demonstrably capable of local immunological reactions, as seen in the jejunum in celiac sprue and in the colon in idiopathic ulcerative colitis. The age-related appearances of atrophy and dedifferentiation are much less obvious than in the stomach. In a study of senile Wistar rats[9] the duodenal villi were reduced in height by about 25%, while epithelial cell renewal, as measured by the H_3TdR labelling index, appeared unchanged. Microchemical determinations of alkaline phosphatase, an indicator of the maturation and differentiation of the epithelial cells, showed much lower than normal adult levels. In a study of small bowel biopsies from 10 healthy human subjects aged 60 to 73 years,[10] estimated mucosal surface area was significantly reduced ($p < 0.001$) below the mean of 10 control subjects aged 16 to 30. The previously mentioned reductions in alkaline phosphatase per unit weight of tissue, plus known or suspected deficiences of lactose and other intracellular enzymes, may be entirely due to the smaller cell population which results from minor but cumulative effects of slowed cell renewal.

These morphological and functional changes in absorptive rates probably lie within the range that can be compensated for by the reserve capacity of the bowel. Malabsorption as a biological function of aging is usually at a level far below the clinical threshold. Malabsorptive states in the aged have nevertheless been repeatedly described, due to such factors as duodenal or jejunal diverticula, chronic pancreatitis, postgastrectomy syndrome, and celiac sprue. Among a large group of unknown origin, it is possible that occlusive vascular disease (see above) is at times the cause.

The most serious consequence of epithelial atrophy and dedifferentiation is almost certainly heightened susceptibility of the mucosa to the action of carcinogens. The association of atrophic gastritis with later emergence of gastric cancer is a prototype of this relationship. In the small and large intestines the more common sites of development of carcinoma are those in which at least some of the surface epithelial cells are immature, retaining the capacity to proliferate,[5] and lacking intracellular enzymes capable of destroying or inactivating common carcinogens.[11]

DEGENERATIVE CHANGES IN CONNECTIVE TISSUE

Age-related changes in connective tissues have long been a major focus of interest for gerontologists, including both clinicians and laboratory investigators. From observation of facial wrinkles and demineralized bones to the study of aged fibroblasts in tissue culture, an abundance of information has been derived about the aging of skeletal structures. Some of it, I believe, may be relevant to an understanding of the aging gut; but, until supported by direct experimentation on the intestinal wall, the implications are wholly hypothetical.

In theory, the properties of connective tissue most critical to the integrity of the gut are those of flexibility and tensile strength; and these properties appear identifiable, among the several structural proteins of connective tissue, with collagen. Various age-related changes in collagen have been described. For one, it becomes more resistant to collagenases. The number or the chemical nature of its crosslinks is altered, rendering it less flexible and reducing its tensile strength—aged connective tissue has been compared to tanned leather.[12]

The resistance of the gut wall to stretch has, in fact, been found to be reduced in one common disease of the elderly, diverticulosis coli, and this despite increased thickness and strength of contraction of the muscular coats.[13] Wherever pseudodiverticula occur in the gut (including the hypopharynx, the descending duodenum, the mesenteric small bowel, and the colon) they are formed by herniation through the principal gaps in the lamina muscularis, where the resistance of the wall to pressure is almost wholly a property of its connective tissue. This aspect of the pathogenesis of diverticular disease has received very little attention from investigators, even though reports of precocious development of diverticula in younger persons with Marfan's or the Ehlers-Danlos syndromes show that experiments of nature are already on the record.[14]

Other gastrointestinal disorders among the elderly may be in part attributable to the aging of connective tissue and its lowered resistance to stretch. The accommodation of the rectum and colon to enormous accumulations of feces is a factor in the development of obstipation, fecal impaction, stercoral ulcer, and anal incontinence; and in this process the properties of collagen may have an effect distinct from the functions of nerve and smooth muscle. The loosening of the mucosa and submucosa leads to prolapse of these layers through the anus on straining and increases the size and secondary complications of hemorrhoids.

NEURONAL DEGENERATION

The ganglia of the myenteric and submucosal plexuses were long ago recognized as an *enteric nervous system,* which antedated in evolutionary development the autonomic nervous system and the brain. Recently, the "visceral brain" has been clearly shown to harbor internuncial neurons, and to share with the "big brain" within the cranium a large and growing number of proved or probable mechanisms of neurotransmission.

Impelled by the phenomena of senile dementia, many investigators have sought and found age-related changes in brain cells, even while discovering they are not the sole determinants of dementia itself. The RNA content of cerebellar neurons declines with age, as does the rate of transcription of DNA ("single-copy" DNA). Multisynaptic transmission is significantly retarded, evidenced especially by the slowed turnover of catecholamines in the hypothalamus and putamen. The age-related phenomena of Parkinson's disease are associated with reduced dopamine levels in the central nervous system. Aging *per se* is also known to affect autonomic mechanisms, at least with respect to thermoregulation and postural changes in vasomotor activity.[15]

It is highly probable *a priori* that the enteric nervous system and the related autonomic pathways share in these senile changes, and that their consequences include some of the persistent abnormalities of gut motility seen in elderly patients. The most fully recognized example of this is the complex of functional and structural changes in the gullet of the aged known as presbyesophagus.[16] Though differing in some details, the findings of several research groups who have studied its motility in very old "normal" subjects include: disordered peristalis in the body of the esophagus—fewer and weaker primary peristaltic waves on swallowing with greater frequency than in younger subjects of uncoordinated "tertiary" contractions and defects in secondary peristalsis as well; diminished relaxation of the lower esophageal sphincter on swallowing; and increased frequency of gastroesophageal reflux. These changes give rise at times to dysphagia, and at other times predispose to reflux exophagitis and hiatal hernia.

Parallel studies of the pharyngoesophageal segment have revealed weakness of the pharyngeal musculature and reduced strength of contraction of the upper esophageal sphincter (the cricopharyngeus muscle), which could increase the likelihood of aspiration of esophageal contents.[17] It is believed by some that uncoordinated contractions of the cricopharyngeus

during deglutition, leading to excessive pressures in the hypopharynx, are a factor in the etiology of Zenker's diverticulum.

Morphological changes in these structures are less well studied but are compatible with the functional abnormalities. Thickening of the esophageal muscle has been often described in presbyesophagus; and a recent careful study[18] confirms an earlier report that the number of myenteric ganglion cells per unit area is significantly smaller in the aged than in younger persons ($p<0.05$). These same anatomic features are associated with an excess of tertiary contractions in younger individuals with so-called "diffuse esophageal spasm" who exhibit pharmacological evidence of autonomic denervation, and the parallel phenomena among the elderly may have a similar explanation.

Elsewhere in the gut, the normal patterns of motility are less predictable, access to recording instruments is often more difficult, and fewer data are available. The frequent complaints of constipation heard from the elderly are not reflected in significant delay in the passage of ingested markers (plastic pellets) in the feces, except in inactive or bedridden individuals.[19] Primary atony of the colonic musculature is probably rare, but anorectal dysfunction of neural origin appears to be common. On the afferent side of the defecation reflex, the mean intrarectal pressure and the mean diameter of the rectum at the threshold of perception were both observed to be progressively greater as age advances, both in constipated and nonconstipated subjects.[20] In at least one form of defecation disorder found in elderly individuals, namely, anal incontinence, reflex contraction of the external anal sphincter fails to occur in response to intrarectal distension. It is less clear whether the same stimulus, which regularly produces relaxation of the internal anal sphincter in healthy younger subjects, may fail to evoke this response in elderly constipated persons. Further study of these responses is of great practical interest because it has been shown that reinforcement of the reflex patterns by instrumental learning (biofeedback) is effective in incontinent persons even in extreme old age.[21]

In a large subset of patients with diverticular disease, several related observations together suggest a primary neuromuscular abnormality of the distal colon. These findings include increased intraluminal pressures, abnormal patterns of myoelectrical activity, and grossly thickened muscular layers of the colonic wall.[14] Some have suggested that these are consequences of disturbed innervation, even aganglionosis, but the hypothesis

has found little support. The age-specific character of the disease and the unchanging nature of the motility disturbances make the idea that senile neuronal degeneration is involved an attractive one, and deserves much more attention than it has yet received.

Finally, this brief review of the most common factors underlying disorders of the aging gut should take account of one not-so-common but eminently treatable secondary phenomenon—bacterial overgrowth within the lumen of the small bowel. This is favored by neuronal degeneration resulting from diabetes mellitus and possibly ischemia of the intestine, which leads to stasis. It may be attributable to scleroderma of the intestine or common duodenal or jejunoileal diverticula. The consequences of the "stasis syndrome" include diarrhea, steatorrhea, and vitamin B_{12} deficiency, all of which can be relieved by appropriate antibiotics in low dosage.

In view of the many gaps in our knowledge which this survey has disclosed and the many ways in which digestive disturbances impair the quality of life enjoyed by our aging population, this field presently offers attractive opportunities for clinical investigation. If this review can serve a truly useful purpose, it should soon be out of date.

SUMMARY

The common digestive disorders of the elderly appear to be the consequences both of biological aging and of chronic diseases of long latency. Ischemia has many manifestations more subtle than infarction of the bowel, and results from local or regional vascular narrowing due to atheroma in addition to cardiac and pulmonary insufficiency. Atrophy and dedifferentiation of the epithelium lead to secretory failure, possibly to malabsorption, and clearly to neoplasia of stomach and colon. Degenerative changes in the collagen of the connective tissue stroma may underlie the development of diverticula in the aged, as well as of megacolon, volvulus, and mucosal prolapse. Fixed patterns of motility disorder in the aged may result from intrinsic neuronal degeneration, with manifestations that include presbyesophagus and impaired defecation reflexes and may contribute to intestinal stasis and diverticulosis coli. The impairments of digestion, absorption, and propulsive motility together contribute to bacterial overgrowth in the gut lumen and the nutritional consequences of the "stasis syndrome."

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